

=> s 4-1BB

L3 272 4-1BB

=> s l3 and activation

L4 150 L3 AND ACTIVATION

=> s l3 and activat?

L5 183 L3 AND ACTIVAT?

=> d ibib abs 1-15

09/26/00

L5 ANSWER 1 OF 183 MEDLINE

ACCESSION NUMBER: 2000401197 MEDLINE

DOCUMENT NUMBER: 20304441

TITLE: Expression of soluble CD137 correlates with
activation-induced cell death of lymphocytes.

AUTHOR: Michel J; Schwarz H

CORPORATE SOURCE: Department of Pathology, University of Regensburg,
Regensburg, Germany.

SOURCE: CYTOKINE, (2000 Jun) 12 (6) 742-6.
Journal code: A52. ISSN: 1043-4666.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200010

ENTRY WEEK: 20001004

AB CD137 is a member of the tumour necrosis factor receptor family which
delivers a potent co-stimulatory signal to T lymphocytes. Soluble forms
of

CD137 (sCD137) can be found at enhanced levels in sera of patients with
rheumatoid arthritis. Here we show that expression of sCD137 lags behind
that of membrane-bound CD137 (mCD137) by about 24 h. In fully
activated lymphocytes, time of maximum increase and level of
expression of sCD137 were at day 2 and 3, respectively. Expression of
sCD137 in lymphocytes requires strong **activation**, and levels of
sCD137 correlate negatively with lymphocyte proliferation and positively
with the degree of **activation**-induced cell death caused by
mitogen overstimulation. Since **activation** of lymphocytes through
membrane-bound CD137 delivers a potent stimulatory signal, sCD137 may
provide a negative control mechanism for immune responses. Copyright 2000
Academic Press.

L5 ANSWER 2 OF 183 MEDLINE

ACCESSION NUMBER: 2000393332 MEDLINE

DOCUMENT NUMBER: 20297157

TITLE: Monoclonal antibodies directed against the T-cell
activation molecule CD137 (interleukin-A or
4-1BB) block human lymphocyte-mediated
suppression of tumor xenografts in severe combined
immunodeficient mice.

AUTHOR: Sabel M S; Conway T F; Chen F A; Bankert R B

CORPORATE SOURCE: Department of Immunology, Roswell Park Cancer Institute,
Buffalo, New York 14263, USA.

CONTRACT NUMBER: CA09581 (NCI)
CA54491 (NCI)
CA75235 (NCI)

+

SOURCE: JOURNAL OF IMMUNOTHERAPY, (2000 May Jun) 23 (3) 362-8.
Journal code: CUQ.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY WEEK: 20001003

AB A monoclonal antibody specific for the human analog of the murine T-cell **activation** molecule **4-1BB** was generated and is shown here to react selectively with **activated** human CD4+ and CD8+ T lymphocytes. Treatment of these T cells in a one-way mixed lymphocyte culture with the anti-h4-1BB antibody enhanced the cell proliferation of the allostimulated lymphocytes. Previous studies in the mouse have shown that treatment of tumor-bearing mice with antibodies to **4-1BB** augments anti-tumor immunity that is mediated by both CD4+ and CD8+ T cells. The authors consider the possibility that a similar approach may be efficacious for human cancer immunotherapy. This question was addressed by evaluating the effect of an anti-h4-1BB monoclonal antibody on human lymphocyte-mediated suppression of a human tumor xenograft in SCID mice. Mice treated with a control antibody and co-injected with the tumor and peripheral blood lymphocytes exhibited a lymphocyte dose-dependent suppression of tumor growth. In mice treated with the anti-h4-1BB antibody, the lymphocyte-mediated tumor suppression was completely eliminated and tumors grew progressively (as was observed in mice inoculated with tumors without lymphocytes). This monoclonal antibody specific for anti-h4-1BB, which augments the proliferation of allostimulated cells in vitro, blocks T-cell anti-tumor activity in vivo. These results suggest that although **4-1BB** plays a role in the human peripheral blood lymphocyte-mediated suppression of tumor growth, antibodies to this molecule on human cells fail to stimulate anti-tumor activity, as was observed in tumor-bearing mice treated with an antibody to murine **4-1BB**.

L5 ANSWER 3 OF 183 MEDLINE
ACCESSION NUMBER: 2000389738 MEDLINE
DOCUMENT NUMBER: 20374250
TITLE: Analysis of expression and function of the costimulatory molecule **4-1BB** in alloimmune responses.
AUTHOR: Tan J T; Ha J; Cho H R; Tucker-Burden C; Hendrix R C; Mittler R S; Pearson T C; Larsen C P
CORPORATE SOURCE: The Carlos and Marguerite Mason Transplantation Biology Research Center and Department of Surgery, Emory University
School of Medicine, Atlanta, GA 30322, USA.
CONTRACT NUMBER: AI-40519 (NIAID)
AI-44644 (NIAID)
SOURCE: TRANSPLANTATION, (2000 Jul 15) 70 (1) 175-83.
Journal code: WEJ. ISSN: 0041-1337.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200010
ENTRY WEEK: 20001002

AB BACKGROUND: **4-1BB** (CD137) is a T cell costimulatory molecule that promotes T cell **activation**. In this study, we investigated the role of **4-1BB** costimulation in allogeneic T cell responses. METHODS: Vascularized heart transplantation, allogeneic mixed leukocyte reaction (MLR), and graft versus host disease models were used to examine **4-1BB** and 4-1BBL expression. In addition, agonistic anti-**4-1BB** antibodies were used in MLR to functionally analyze T cell responses. RESULTS: Using a heart transplant model, we found that **4-1BB** and 4-1BBL transcripts were both expressed in rejecting cardiac grafts. In the allogeneic MLR, **4-1BB** was expressed on both **activated** CD4 and CD8 T cells and **4-1BB** was expressed on T cells after multiple cell divisions in

vivo. Functionally, **4-1BB** was a potent stimulator of proliferation, cytokine secretion, and CD25 expression by CD8 T cells, but

4-1BB signals had a weak effect on the proliferation of CD4 T cells. Because **4-1BB** promoted the secretion of IL-2 and the expression of CD25 on CD8 T cells, we investigated whether IL-2 was the only factor whereby **4-1BB** signals induced CD8 T cell proliferation. Although IL-2 was required for optimal CD8 T cell proliferation, **4-1BB** also costimulated CD8 T cell proliferation independently of IL-2. CONCLUSIONS: This study demonstrates that **4-1BB** is expressed on **activated**, maximally divided T cells and shows that **4-1BB** promotes CD8 T cell proliferation by enhancing signals through the IL-2 receptor and by other mechanisms independent of the IL-2 pathway.

L5 ANSWER 4 OF 183 MEDLINE

ACCESSION NUMBER: 2000334238 MEDLINE

DOCUMENT NUMBER: 20334238

TITLE: Comparative analysis of CD137 and LPS effects on monocyte **activation**, survival, and proliferation.

AUTHOR: Langstein J; Becke F M; Sollner L; Krause G; Brockhoff G; Kreutz M; Andreesen R; Schwarz H

CORPORATE SOURCE: Department of Pathology, University of Regensburg, Regensburg, 93042, Germany.

SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Jun 24) 273 (1) 117-22.

Journal code: 9Y8. ISSN: 0006-291X.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 200009

ENTRY WEEK: 20000905

AB CD137 (ILA/**4-1BB**), a member of the TNF receptor family, regulates **activation**, survival and proliferation of primary human monocytes. Here we compare the activities of lipopolysaccharide (LPS), a classical and potent monocyte **activator** to that of CD137. LPS is a more potent **activator** of monocytes, as evidenced by a stronger induction of the proinflammatory cytokine IL-8. However, CD137 could further increase maximal cytokine induction by LPS, which points to separate signaling pathways for LPS and CD137. Also, expression of myc was only induced by the combination of CD137 and LPS. Expression of macrophage colony-stimulating factor is induced more potently by CD137, but an additive effect is obtained by the combination of CD137 and LPS. Monocyte/macrophage survival and proliferation is only induced by CD137. LPS counteracts both activities of

CD137 via **activation** induced cell death. While LPS has a role in **activation** of monocytes in innate immunity, the CD137 receptor/ligand system seems to deliver an **activating** signal to monocyte in acquired immunity. Copyright 2000 Academic Press.

L5 ANSWER 5 OF 183 MEDLINE

ACCESSION NUMBER: 2000318386 MEDLINE

DOCUMENT NUMBER: 20318386

TITLE: Translocation of TRAF proteins regulates apoptotic threshold of cells.

AUTHOR: Arch R H; Gedrich R W; Thompson C B

CORPORATE SOURCE: Gwen Knapp Center for Lupus and Immunology Research, Howard

Hughes Medical Institute, Department of Medicine, University of Chicago, IL 60637, USA.. rarch@im.wustl.edu
BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Jun 16) 272 (3) 936-45.

Journal code: 9Y8. ISSN: 0006-291X.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 200009
ENTRY WEEK: 20000905

AB Tumor necrosis factor (TNF) receptor-associated factors (TRAFs) are involved in signaling pathways triggered by members of the TNF receptor (TNFR) family and other cell surface proteins. After recruitment to a receptor, TRAFs initiate formation of multiprotein complexes that induce downstream events, such as translocation of transcription factor nuclear factor kappaB (NF-kappaB) and **activation** of c-Jun N-terminal kinase (JNK). Several proteins in these complexes play important roles in regulation of apoptosis. However, the fate of TRAF-containing complexes once assembled in response to receptor multimerization is not understood. In this report, we demonstrate that crosslinking of TNFR family members

or

interaction of TRAF2 with the cytoplasmic protein A20 leads to intracellular translocation of TRAF2. This redistribution leads to depletion of the cytoplasmic pool of TRAF2. The ratio between soluble and insoluble TRAF2 determines the sensitivity of cells to TNF-alpha-induced apoptosis and may play an important role in limiting further TRAF-dependent signal transduction. Copyright 2000 Academic Press.

L5 ANSWER 6 OF 183 MEDLINE

ACCESSION NUMBER: 2000302863 MEDLINE

DOCUMENT NUMBER: 20302863

TITLE: Immunomodulatory gene therapy with interleukin 12 and 4-1BB ligand: long-term remission of liver metastases in a mouse model.

AUTHOR: Martinet O; Ermekova V; Qiao J Q; Sauter B; Mandeli J; Chen

L; Chen S H

CORPORATE SOURCE: Institute for Gene Therapy and Molecular Medicine, The Mount Sinai School of Medicine, New York, NY 10029-6574, USA.

CONTRACT NUMBER: CA70330 (NCI)
CA75175 (NCI)
CA84404 (NCI)

SOURCE: JOURNAL OF THE NATIONAL CANCER INSTITUTE, (2000 Jun 7) 92 (11) 931-6.

Journal code: J9J. ISSN: 0027-8874.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 200009

ENTRY WEEK: 20000904

AB BACKGROUND: The success of immunomodulatory cancer therapy is frequently hampered by the transient nature of the antitumor immune response. We have

shown previously in a mouse model that interleukin 12 (IL-12) generates a strong natural killer (NK) cell-mediated antitumor response and reduces liver metastases induced by a colon carcinoma cell line. However, only a small percentage of the treated animals developed the cytotoxic T-lymphocytic response required for a long-term systemic antitumor immunity. 4-1BB is a co-stimulatory molecule expressed on the surface of **activated** T cells. Interaction of 4-1BB with its natural ligand (4-1BBL) has been shown to amplify T-cell (especially CD8+)-mediated immunity. In this study, we

investigated

the effects of adenovirus-mediated gene therapy delivering both IL-12 and 4-1BBL genes on mice with hepatic metastases induced by colon cancer cells. METHODS: Syngeneic BALB/c mice received intrahepatic injection of poorly immunogenic MCA26 colon cancer cells. Various combinations of replication-defective adenoviruses expressing IL-12 and 4-1BBL genes were injected into the established liver tumors. Changes in tumor size and animal survival were then monitored. All statistical tests were

two-sided.

RESULTS: The long-term survival rate of mice treated with the combination of IL-12 and 4-1BBL was significantly improved over that of animals in

the

control group (P = .0001). In vivo depletion of NK cells or CD8+ T cells

completely abolished the long-term survival advantage of the IL-12 plus 4-1BBL-treated animals (P<.002). Moreover, the systemic immunity induced by this combination treatment protected these animals against a subcutaneous challenge with parental MCA26 cells. CONCLUSION: Adenovirus-mediated transfer of IL-12 and 4-1BBL genes directly into liver tumors resulted in tumor regression that required both NK and CD8+ T cells and generated a potent, long-lasting antitumor immunity.

L5 ANSWER 7 OF 183 MEDLINE

ACCESSION NUMBER: 2000256302 MEDLINE

DOCUMENT NUMBER: 20256302

TITLE: Gene structure and chromosomal assignment of mouse GITR, a member of the tumor necrosis factor/nerve growth factor receptor family.

AUTHOR: Nocentini G; Bartoli A; Ronchetti S; Giunchi L; Cupelli A; Delfino D; Migliorati G; Riccardi C

CORPORATE SOURCE: Department of Clinical and Experimental Medicine, Perugia University Medical School, Italy.

SOURCE: DNA AND CELL BIOLOGY, (2000 Apr) 19 (4) 205-17.
Journal code: AF9. ISSN: 1044-5498.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200007

ENTRY WEEK: 20000704

AB GITR is a type I transmembrane protein that belongs to the tumor necrosis factor/nerve growth factor receptor (TNF/NGFR) family. This receptor is preferentially expressed in **activated** T lymphocytes and may function as signaling molecule during T-cell development. In the present study, we examined the genomic organization of the entire mouse GITR (mGITR) gene. The gene spans a 2543-bp region and consists of five exons (with a length ranging from 88 bp to 395 bp) and four introns (67 bp to 778 bp). In agreement with GITR expression in **activated** T cells, consensus elements for transcription factors involved in T-cell development and **activation** were identified in the 5' flanking region, including a consensus element for NF-kappaB. Two highly significant binding sites for MyoD and one binding site for myogenin were also found, suggesting involvement of GITR in muscle development. The mGITR gene contains 17 transcription initiation sites distributed over a 76-bp region, all used with the same frequency. We localized mGITR to the murine chromosome 4 (E region), where other 4 TNF/NGFR members localize, including m4-1BB and mOX40. These results further indicate that GITR shares several features with OX40, **4-1BB**, and CD27, suggesting the existence of a new subfamily of the TNFR family, as also confirmed by the similarity of their cytoplasmic domains.

L5 ANSWER 8 OF 183 MEDLINE

ACCESSION NUMBER: 2000143821 MEDLINE

DOCUMENT NUMBER: 20143821

TITLE: **4-1BB** costimulation is required for protective anti-viral immunity after peptide vaccination.

AUTHOR: Tan J T; Whitmire J K; Murali-Krishna K; Ahmed R; Altman J D; Mittler R S; Sette A; Pearson T C; Larsen C P

CORPORATE SOURCE: The Carlos and Marguerite Mason Transplantation Biology Research Center and Department of Surgery, Emory University

School of Medicine, Atlanta, GA 30322, USA.

CONTRACT NUMBER: AI40519 (NIAID)

AI44644 (NIAID)

AI30048 (NIAID)

+

SOURCE: JOURNAL OF IMMUNOLOGY, (2000 Mar 1) 164 (5) 2320-5.
Journal code: IFB. ISSN: 0022-1767.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 200005
ENTRY WEEK: 20000504

AB Peptide vaccination induces T cell **activation** and cytotoxic T cell development. In an effort to understand what factors can improve immune responses to peptide vaccination, the role of **4-1BB** (CD137) costimulation was examined, since **4-1BB** has been shown to promote T cell responses in other systems. **4-1BBL**-deficient (-/-) and wild-type (+/+) mice were immunized with a lipidated lymphocytic choriomeningitis virus (LCMV) peptide NP396-404. Analysis of peptide-specific responses early after immunization by CTL assay, intracellular IFN-gamma staining, and IFN-gamma enzyme-linked immunospot assay (ELISPOT) indicated that CD8 T cell responses were reduced 3- to 10-fold in the absence of **4-1BB** costimulation. Moreover, when agonistic anti-**4-1BB** Ab was given, CD8 T cell responses in **4-1BBL**-/- mice were augmented to levels similar to those in **4-1BBL**+/+ mice. Two months after immunization, **4-1BBL**+/+ mice still had epitope-specific cells and were protected against viral challenge, demonstrating that peptide vaccination can induce long-term protection. In fact, 70% of CD8 T cells were specific for the immunizing peptide after viral challenge, demonstrating that strong, epitope-specific CD8 T cell responses are generated after peptide vaccination. In contrast, peptide-immunized **4-1BBL**-/- mice had fewer epitope-specific cells and were impaired in their ability to resolve the infection. These results show that immunization with a single LCMV peptide provides long term protection against LCMV infection and point to costimulatory molecules such as **4-1BB** as important components for generating protective immunity after vaccination.

L5 ANSWER 9 OF 183 MEDLINE

ACCESSION NUMBER: 2000135841 MEDLINE
DOCUMENT NUMBER: 20135841
TITLE: Co-stimulation of antigen-specific CD4 T cells by **4-1BB** ligand.
AUTHOR: Gramaglia I; Cooper D; Miner K T; Kwon B S; Croft M
CORPORATE SOURCE: La Jolla Institute for Allergy and Immunology, Division of Immunochemistry, San Diego 92121, USA.
CONTRACT NUMBER: AI36259 (NIAID)
AI42944 (NIAID)
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Feb) 30 (2) 392-402.
Journal code: EN5. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200005
ENTRY WEEK: 20000503

AB **4-1BB** is a member of the TNF receptor family predominantly expressed on **activated** T cells, and binds an inducible ligand found on B cells, macrophages and dendritic cells. Whereas ligation of **4-1BB** has been shown to enhance response of purified CD8 T cells to mitogens, and to augment NK activity and generation of cytotoxic T lymphocytes in vivo, there are little direct data on **4-1BB** action during CD4 responses. Using pigeon cytochrome c-presenting fibroblast antigen-presenting cells transfected with **4-1BB** ligand (**4-1BBL**), we show that engaging **4-1BB** on naive CD4 cells promotes proliferation, cell cycle progression and IL-2 secretion, and suppresses cell death, all to a similar extent as B7-1 engagement of CD28. In addition, **4-1BBL** synergizes with B7 and ICAM to enhance naive CD4 proliferation when antigen is limiting. **4-1BBL** alone, and to a greater extent with B7, also augmented IL-2 secretion resting antigen-experienced CD4 cells, as typified by T helper clones, whereas short-term effector cells showed similar levels of proliferation and cytokine secretion

regardless of whether **4-1BB** was engaged. A major role in augmenting IFN- γ , IL-4 or IL-5 was not demonstrated. Blocking studies with **activated** B cells presenting antigen showed that **4-1BB** participates in promoting IL-2 production by resting CD4 cells, confirming that **4-1BBL** can play a role in antigen-specific CD4 T cell responses.

L5 ANSWER 10 OF 183 MEDLINE

ACCESSION NUMBER: 2000076289 MEDLINE

DOCUMENT NUMBER: 20076289

TITLE: CD137 (ILA/**4-1BB**), expressed by primary human monocytes, induces monocyte **activation** and apoptosis of B lymphocytes.

AUTHOR: Kienzle G; von Kempis J

CORPORATE SOURCE: Division of Rheumatology and Clinical Immunology, University Hospital Department of Medicine, Hugstetter Strasse 55, 79106 Freiburg, Germany.

SOURCE: INTERNATIONAL IMMUNOLOGY, (2000 Jan) 12 (1) 73-82.
Journal code: AY5. ISSN: 0953-8178.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200004

ENTRY WEEK: 20000404

AB Human CD137 is a member of the tumor necrosis factor (TNF) receptor family

and the homologue of murine **4-1BB**. Recent studies have demonstrated that CD137 promotes accessory T cell **activation**, and regulates proliferation and survival of T lymphocytes. This study reports on the expression and function of CD137 in peripheral blood monocytes. While monocytes showed constitutive expression in 10 out of 18 healthy donors, CD137 was not expressed on resting T or B lymphocytes. Immobilized antibodies to CD137 markedly induced the production of IL-8 and TNF- α protein and mRNA, and led to inhibition of IL-10 expression by primary monocytes. Furthermore, cross-linking of CD137 on monocytes resulted in an increase of B lymphocyte apoptosis mediated by direct cell-cell contact of both cell populations. In conclusion, this study identified CD137 as a new receptor involved in monocyte **activation** by inducing a characteristic cytokine release profile. In addition, CD137 may play a role in monocyte-dependent control of B lymphocyte survival.

L5 ANSWER 11 OF 183 MEDLINE

ACCESSION NUMBER: 2000067721 MEDLINE

DOCUMENT NUMBER: 20067721

TITLE: Biochemical and immunological characteristics of **4-1BB** (CD137) receptor and ligand and potential applications in cancer therapy.

AUTHOR: Sica G; Chen L

CORPORATE SOURCE: Department of Immunology, Mayo Clinic, Rochester, Minnesota

55905, USA.

SOURCE: ARCHIVUM IMMUNOLOGIAE ET THERAPIAE EXPERIMENTALIS, (1999) 47 (5) 275-9. Ref: 39

Journal code: 790. ISSN: 0004-069X.

PUB. COUNTRY: Poland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY WEEK: 20000304

AB **4-1BB** (CD 137) is a member of the tumor necrosis factor receptor (TNFR) superfamily that is expressed primarily on **activated** T cells. Crosslinking of the **4-1BB** receptor **activates** an intracellular signal cascade that leads to the **activation** of NF- κ B and costimulation of T cell growth. Recent evidence indicates that **4-1BB** may

preferentially co-stimulate CD8+ T cell growth and induce cytolytic activity. The cytolytic activity induced by **4-1BB** crosslinking is able to eradicate large, well-established, poorly immunogenic tumors and augments allogenic T cell responses in vivo. The **4-1BB/4-1BB** ligand costimulatory pathway can provide an alternative T cell costimulatory pathway in the absence of CD28, but may physiologically function as a synergistic or complementary pathway to the CD28 costimulatory pathway. Only some of the basic immunological functions of **4-1BB/4-1BB** ligand have been elucidated and much study is required to determine its exact role in T cell **activation**.

L5 ANSWER 12 OF 183 MEDLINE

ACCESSION NUMBER: 2000029812 MEDLINE

DOCUMENT NUMBER: 20029812

TITLE: Anti-**4-1BB** monoclonal antibodies abrogate T cell-dependent humoral immune responses in vivo through the induction of helper T cell anergy.

AUTHOR: Mittler R S; Bailey T S; Klussman K; Trailsmith M D; Hoffmann M K

CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Department of Immunology and Transplantation, Seattle, Washington 98121, USA.. Rmittler26@aol.com

SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1999 Nov 15) 190 (10) 1535-40.

Journal code: I2V. ISSN: 0022-1007.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 200002

ENTRY WEEK: 20000204

AB The **4-1BB** receptor (CDw137), a member of the tumor necrosis factor receptor superfamily, has been shown to costimulate the **activation** of T cells. Here we show that anti-mouse **4-1BB** monoclonal antibodies (mAbs) inhibit thymus-dependent antibody production by B cells. Injection of anti-**4-1BB** mAbs into mice being immunized with cellular or soluble protein antigens induced long-term anergy of antigen-specific T cells. The immune response to the type II T cell-independent antigen trinitrophenol-conjugated Ficoll, however, was not suppressed. Inhibition of humoral immunity occurred only when anti-**4-1BB** mAb was given within 1 wk after immunization. Anti-**4-1BB** inhibition was observed in mice lacking functional CD8(+) T cells, indicating that

CD8(+) T cells were not required for the induction of anergy. Analysis of the requirements for the anti-**4-1BB**-mediated inhibition of humoral immunity revealed that suppression could not be adoptively transferred with T cells from anti-**4-1BB**-treated mice. Transfer of BALB/c splenic T cells from sheep red blood cell (SRBC)-immunized and anti-**4-1BB**-treated mice together with normal BALB/c B cells into C.B-17 severe combined immunodeficient mice failed to generate an anti-SRBC response. However, B cells from the SRBC-immunized, anti-**4-1BB**-treated BALB/c mice, together with normal naive T cells, exhibited a normal humoral immune response against SRBC after transfer, demonstrating that SRBC-specific B cells were left unaffected by anti-**4-1BB** mAbs.

L5 ANSWER 13 OF 183 MEDLINE

ACCESSION NUMBER: 1999458943 MEDLINE

DOCUMENT NUMBER: 99458943

TITLE: **4-1BB** ligand, a member of the TNF family, is important for the generation of antiviral CD8 T cell responses.

AUTHOR: Tan J T; Whitmire J K; Ahmed R; Pearson T C; Larsen C P

CORPORATE SOURCE: The Carlos and Marguerite Mason Transplantation Biology Research Center, Department of Surgery, Emory University School of Medicine, Atlanta, GA 30322, USA.

CONTRACT NUMBER: AI/DK40519-01 (NIAID)

AB 0048 (NIAID)
NS 1496 (NINDS)
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Nov 1) 163 (9) 4859-68.
Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 200001
ENTRY WEEK: 20000104

AB 4-1BB (CD137) is a costimulatory molecule expressed on **activated** T cells and interacts with 4-1BB ligand (4-1BBL) on APCs. To investigate the role of 4-1BB costimulation for the development of primary immune responses, 4-1BBL-deficient (4-1BBL-/-) mice were infected with lymphocytic choriomeningitis virus (LCMV). 4-1BBL-/- mice were able to generate CTL and eliminate acute LCMV infection with normal kinetics, but CD8 T cell expansion was 2- to 3-fold lower than in wild-type (+/+) mice. In the same mice, virus-specific CD4 Th and B cell responses were minimally affected, indicating that 4-1BB costimulation preferentially affects CD8 T cell responses. This result contrasts with our earlier work with CD40L-deficient (CD40L-/-) mice, in which the CD8 T cell response was unaffected and the CD4 T cell response was markedly impaired. When both 4-1BBL- and B7-dependent signals were absent, CD8 T cell expansion was further reduced, resulting in lower CTL activity and impairing their ability to clear LCMV. Altogether, these results indicate that T cells have distinct costimulatory requirements: optimal CD8 responses require 4-1BBL-dependent interactions, whereas CD4 responses are minimally affected by 4-1BB costimulation, but require CD40-CD40L and B7-dependent interactions.

L5 ANSWER 14 OF 183 MEDLINE

ACCESSION NUMBER: 1999458940 MEDLINE

DOCUMENT NUMBER: 99458940

TITLE: Analysis of 4-1BB ligand (4-1BBL)-deficient mice and of mice lacking both 4-1BBL and

CD28 reveals a role for 4-1BBL in skin allograft rejection and in the cytotoxic T cell response to influenza virus.

AUTHOR: DeBenedette M A; Wen T; Bachmann M F; Ohashi P S; Barber B H; Stocking K L; Peschon J J; Watts T H

CORPORATE SOURCE: Department of Immunology, University of Toronto, Ontario, Canada.

SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Nov 1) 163 (9) 4833-41.
Journal code: IFB. ISSN: 0022-1767.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals

ENTRY MONTH: 200001

ENTRY WEEK: 20000104

AB 4-1BB ligand (4-1BBL) is a member of the TNF family expressed on **activated** APC. 4-1BBL binds to 4-1BB (CD137) on **activated** CD4 and CD8 T cells and in conjunction with strong signals through the TCR provides a CD28-independent costimulatory signal leading to high level IL-2 production by primary resting T cells. Here we report the immunological characterization of mice lacking 4-1BBL and of mice lacking both 4-1BBL and CD28. 4-1BBL-/- mice mount neutralizing IgM and IgG responses to vesicular stomatitis virus that are indistinguishable from those of wild-type mice. 4-1BBL-/- mice show unimpaired CTL responses to lymphocytic choriomeningitis virus (LCMV) and exhibit normal skin allograft rejection but have a weaker CTL response to influenza virus

than wild-type mice. 4-1BBL-/-CD28-/- mice retain the CTL response to LCMV,

respond poorly to influenza virus, and exhibit a delay in skin allograft rejection. In agreement with these in vivo results, allogeneic CTL responses of CD28^{-/-} but not CD28^{+/+} T cells to 4-1BBL-expressing APC are substantially inhibited by soluble 4-1BB receptor as is the in vitro secondary response of CD28⁺ T cells to influenza virus peptides. TCR-transgenic CD28^{-/-} LCMV glycoprotein-specific T cells are insensitive to the presence of 4-1BBL when a wild-type peptide is used, but the response to a weak agonist peptide is greatly augmented by the presence of 4-1BBL. These results further substantiate the idea that different immune responses vary in their dependence on costimulation and suggest a role for 4-1BBL in augmenting suboptimal CTL responses in vivo.

L5 ANSWER 15 OF 183 MEDLINE

ACCESSION NUMBER: 1999421805 MEDLINE

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TITLE: Dendritic cells generated either from CD34⁺ progenitor cells or from monocytes differ in their ability to **activate** antigen-specific CD8⁺ T cells.

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AB Dendritic cells (DC) can be generated in vitro from monocytes (M-DC) or from CD34⁺ hemopoietic progenitor cells (CD34-DC) but their precursors are

not equivalent cells, prompting a comparison of the functional capacities of these APC. Both types of DCs established from the same individuals using the same cytokines displayed a comparable phenotype of mature DC (CD1a⁺, CD83⁺, CD86⁺, CD4⁺, HLA-DR⁺⁺, CD14⁻, CD15⁻) and were equally potent stimulators of allogeneic T cell proliferation, being both more powerful than immature M-DCs. An autologous panel of APCs produced in HLA-A2⁺ individuals, including CD34-DC, M-DC, monocytes, and EBV-lymphoid cell line was comparatively evaluated for presentation of the Erb-B2 peptide E75 to a CTL line. After short exposures (5 h) to E75-loaded APCs, similar levels of intracellular IFN-gamma were induced in Ag-specific CD8⁺

T cells regardless of APC type. In sustained cultures (4-14 days), more Ag-specific T cells were obtained when peptide was presented on CD34-DC

(p < 0.05) rather than on M-DC, EBV-lymphoid cell lines, or monocytes, and these effects were dose-dependent. **Activated** T cells expressed

4-1BB, and the presence of **4-1BB-Ig**

fusion protein partially blocked Ag-specific CD8⁺ cell **activation**

after CD34-DC or M-DC presentation. Our results show that 34-DC have a preferential capacity to **activate** CD8⁺ T cells and that this

property is not strictly correlated to their ability to induce allogeneic T cell proliferation but due to mechanisms that remain to be defined.

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